

Asthma is associated with increased probability of needing CPAP in children with severe obstructive sleep apnea

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Abstract

Objective: Initiation of continuous positive airway pressure (CPAP) in children with severe obstructive sleep apnea syndrome (OSAS) is challenging and the distinct features of the subset of children requiring CPAP are poorly defined. Asthma often coexists with OSAS in children. The goal of this study was to explore the influence of asthma in the need for CPAP therapy in children with severe OSAS.

Hypothesis: Asthmatic children with severe OSAS have higher probability of needing CPAP than children with severe OSAS without asthma.

Methods: Cross-sectional study of clinical presentation, individual risk factors, and initial overnight polysomnogram (PSG) parameters in children with severe OSAS. Severe OSAS was defined as an obstructive apnea hypopnea index ≥ 10 /h. The association between asthma and CPAP initiation was studied individually and adjusted by pertinent covariates.

Results: Four hundred eligible children (mean age 7 years, $\pm$ SD 5.3) with severe OSAS were enrolled and 133 individuals (33%) were identified to have asthma. The proportion of children needing CPAP was significantly higher in asthmatics with severe OSAS (29%) compared to those with OSAS alone (14%) ($P < 0.01$). Multivariate analysis demonstrated that the association between asthma and the need of CPAP in pediatric severe OSAS was independent of demographics, OSAS severity, obesity, and history of adenotonsillectomy ($P < 0.01$).

Conclusion: Asthmatic children with severe OSAS have higher probability of needing CPAP independent of relevant covariables. This study further substantiates the link between OSAS and asthma in children and suggests the diagnosis of asthma may influence the need of CPAP therapy for severe OSAS.

KEYWORDS

continuous positive airway pressure, obstructive sleep apnea syndrome, pediatric asthma

Abbreviations: AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; NREM, non-rapid-eye movement sleep; OAH, obstructive apnea-hypopnea index; OSAS, obstructive sleep apnea syndrome; PSG, polysomnogram; REM sleep, rapid-eye movement sleep; SaO₂, pulse-oximetry saturation.

1 | INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a disorder of breathing during sleep characterized by recurrent episodes of complete or partial

upper airway obstruction that interrupt nocturnal ventilation and alter normal sleep architecture.^{1,2} The prevalence of pediatric OSAS can vary depending on diagnostic criteria, but it has been estimated to be approximately 3%.³ Interestingly, our group and other research teams have reported that asthma often coexist with OSAS and influences its severity and nocturnal phenotypical features.^{4–8} There is also growing evidence that continuous positive airway pressure (CPAP) in adults and adenotonsillectomy (AT) in children may improve asthma control,^{9–13} suggesting an important bi-directional link between asthma and OSAS. However, it is currently unknown if asthma may also influence the type of therapy required in children with severe OSAS. Specifically, it is unclear if asthmatic children with severe OSAS are more likely to need CPAP after AT, the recommended first line treatment for pediatric OSAS.^{14,15} The goal of this study was to test the hypothesis that asthma is associated with higher probability of needing CPAP therapy in children diagnosed with OSAS by overnight polysomnogram (PSG).

2 | METHODS

2.1 | Study design and procedures

We conducted an analytical single-center cross-sectional study that included patients aged 0–20 years with a diagnosis of severe OSAS according to overnight PSG conducted in the Pediatric Sleep Center of Children's National in Washington D.C. between September 2015 and June 2017 ($n = 400$). Primarily, we tested the hypothesis that asthma is associated with higher probability of needing CPAP therapy in children diagnosed with OSAS by overnight polysomnogram (PSG). Secondary analyses examined if the link between asthma and need for CPAP therapy in children with severe OSAS was independent of individual demographic factors and obesity, which play a role in the pathogenesis of both conditions.^{16–18} We conducted further analysis in the subgroup of children with severe OSAS that underwent AT to determine if asthmatic children with severe OSAS were more likely to require CPAP therapy in this population as well. In addition, we contrasted PSG data of asthmatic and non-asthmatic study subjects to explore potential nocturnal phenotypical features (eg, hypoxemia or REM OSA), clinical presentation (eg, excessive daytime sleepiness), and other comorbidities (eg, rhinitis) that might be associated with need of CPAP therapy in children with severe OSA.

Severe OSA was defined as an obstructive apnea hypopnea index (OAHI) of ≥ 10 events per hour based on initial overnight PSG. We used electronic medical record review to characterize initial clinical presentation, asthma status, individual risk factors, and initial overnight PSG parameters in pediatric individuals with severe OSA. Patients without complete clinical and polysomnographic data available were excluded from the study. This study was approved by the Institutional Review Board of Children's National Health System, Washington, DC. All study patients underwent overnight PSG and scored according to American Academy of Sleep Medicine (AASM) standardized criteria.¹⁹ OAHI and respiratory data were calculated for non-REM and REM sleep. The OAHI included the sum of obstructive apneas, hypopneas and mixed apneas divided by total sleep time. The

minimum respiratory event duration was at least two breaths. Obstructive apneas, mixed apneas, and obstructive hypopneas were scored according to standard guidelines provided by AASM.

2.1.1 | Asthma status and other co-variables

We collected data on clinical and demographic variables from electronic medical records in Children's National Health System, Washington, DC. "Asthma" was identified if previously diagnosed by a physician and using asthma therapy or having asthma symptoms in the past 12 months. Data on other co-variables including age, race, sex, body mass index (BMI), and rhinitis were also collected. "Obesity" was defined as BMI > 95th percentile for the given age and gender based on CDC criteria.²⁰ The variable "rhinitis" was defined as physician diagnosed rhinitis as previously described.²¹

2.2 | Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation (SD) or median interquartile range (IQR), whichever is appropriate. Categorical variables are presented as numbers (percentage). Differences between continuous variables were analyzed using the unpaired *t*-test or the Mann-Whitney U test, whichever was appropriate. Associations between categorical variables were analyzed using the chi-square test or Fisher's exact test, whichever was appropriate. To examine the link between need for CPAP (binary outcome) and asthma (predictor) we built logistic regression models and adjusted for possible confounders such as gender, age, and BMI. All statistical tests were two-tailed, and the significance level used was $P < 0.05$. The data were analyzed with the Stata Statistical Package 12.0 (Stata Corporation, College Station, TX).

3 | RESULTS

3.1 | Study population

Included in this study were 400 children and adolescents (0–20 years). A total of 133 children with severe OSAS (33%) were identified to have asthma. Comparison of demographic and anthropometric variables between asthmatic and non-asthmatic children with severe OSAS is shown in Table 1. Asthmatic children with severe OSAS were more likely to be male, black and obese, which is a demographic pattern known in this population.^{22,23} Age was also significantly higher in asthmatic group (9 years in asthmatic vs 7.4 years in non-asthmatic; $P = 0.004$).

3.2 | Asthmatic children with severe OSAS are more likely to need CPAP therapy relative to children with severe OSAS alone

We first compared the proportion of children with severe OSAS needing CPAP therapy in asthmatic and non-asthmatic individuals. As illustrated in Figure 1A, the proportion of individuals needing CPAP

TABLE 1 Baseline characteristics of children with severe OSA compared in subjects with and without asthma (SD = standard deviation, BMI = body mass index)

	Asthma (n = 133)	No asthma (n = 267)	P-value
Age (mean $\pm$ SD)	9.0 $\pm$ 5.2	7.4 $\pm$ 5.3	0.004
Gender (males %)	67.7	58	0.062
Ethnicity (%)			
White	5.3	15.4	0.003
Black	65.4	50.9	0.006
Hispanic	22.5	19.8	0.532
Others	6.8	13.9	
BMI percentile (mean $\pm$ SD)	83.5 $\pm$ 28.9	73.1 $\pm$ 33.9	0.002

was significantly higher in asthmatics with severe OSAS (29%) compared to children with OSAS alone (14%) ($P = 0.001$). The calculated odds ratio (OR) of needing CPAP in asthmatic children with severe OSAS relative to children with OSAS alone was 2.48 (95% CI 1.48 to 4.15). Extended multivariate analysis revealed that after adjusting for demographic factors, obesity and OSAS severity (according to absolute OAHl value) the association between asthma and the need for CPAP in children with severe OSAS was statistically significant (adjusted OR = 2.33; 95% CI 1.30 to 4.20; $P = 0.005$). Older age and increased OSAS severity were also associated with need of CPAP therapy in children with severe OSAS (Table 2). SaO₂ nadir and stage-specific indices (REM OAHl and NREM OAHl) were independent predictors of CPAP need as well ($P < 0.01$).

3.3 | Asthmatic children with severe OSAS are more likely to need CPAP therapy after AT

AT is the recommended first line treatment for pediatric OSAS. Accordingly, we identified that 46.5% ($n = 186$) of children with severe OSAS underwent AT in our study. The proportion of AT due to severe OSAS was comparable in children with asthma versus non-asthmatic children (48.1% in asthma group vs 46.7% in non-asthmatic children, $P = 0.8$). We conducted additional analysis among children who

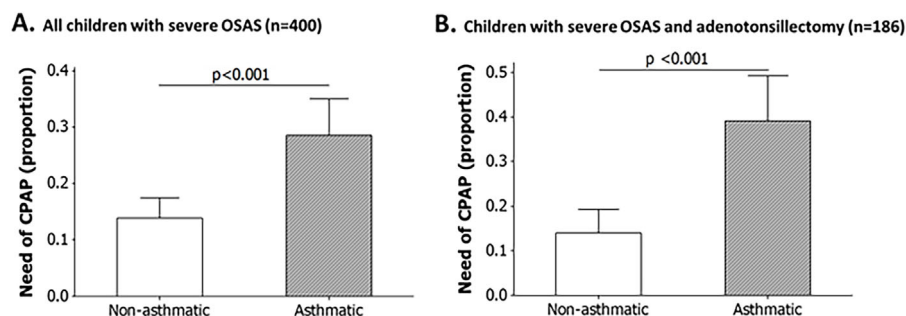
TABLE 2 Multivariable logistic regression analysis results for the association between asthma and need of CPAP in children with severe OSAS adjusted by covariates (SE, standard error; OAHl, obstructive apnea hypopnea index)

Predictor	Parameter estimate	SE	P-value
Asthma	0.846873	0.300095	0.005
Age	0.121724	0.031124	<0.001
OAHl	0.014475	0.004945	0.003
Gender	0.549286	0.323342	0.089
Ethnicity	-0.14872	0.172591	0.389
Obesity	0.295473	0.342752	0.389

underwent AT to determine if asthmatic children with severe OSAS were more likely to require CPAP therapy than individuals without asthma. As shown in Figure 1B, the proportion of individuals needing CPAP was significantly higher in asthmatics with severe OSAS (39%) compared to children with OSAS alone (14%) ($P < 0.001$). Overall, after AT, asthmatic children with severe OSA had more than three times higher probability of requiring CPAP therapy than children with OSA alone (OR = 3.31; 95% CI 1.72 to 6.38). The association between asthma and need of CPAP after AT in children with severe OSAS was significant after adjusting for age, gender, ethnicity, obesity, and OAHl (adjusted OR = 2.78; 95% CI 1.36 to 5.69; $P = 0.005$).

3.4 | PSG features and clinical characteristics of asthmatic children with severe OSAS and need for CPAP therapy

We next contrasted the PSG data and clinical presentation of asthmatic and non-asthmatic study subjects requiring CPAP therapy. We identified that indices of overall severity (OAHl), severity by sleep stage (REM OAHl and NREM OAHl), and maximal SaO₂ desaturation were greater in children with severe OSAS that required CPAP but were unaffected by individual asthma status (Figures 2A and 2B). In terms of symptoms reported during initial evaluation, we identified that individuals with severe OSAS with or without asthma had similar clinical presentation including snoring, apnea/gasping, and daytime attention deficit/hyperactivity (Figure 3). Interestingly, excessive

**FIGURE 1** Comparison of the proportion of children with severe OSAS needing CPAP therapy in asthmatic and non-asthmatic individuals: (A) overall study population. (B) Children who had adenotonsillectomy

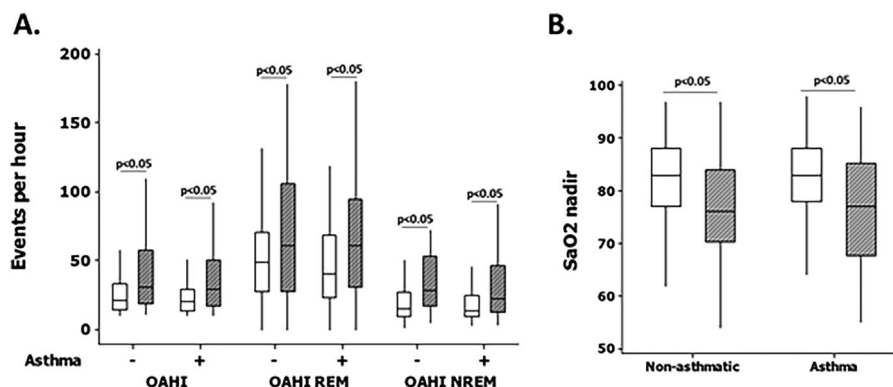


FIGURE 2 Comparison of the PSG data of asthmatic and non-asthmatic study subjects requiring CPAP therapy after adenotonsillectomy: (A) OAH (total, REM, and NREM) and (B) Sao2 nadir compared in both groups

daytime sleepiness (EDS) was significantly more frequent among children with severe OSAS and asthma (asthma group 47% vs non-asthma group 32%; $P = 0.003$). Moreover, as shown in Figure 4A, asthmatic children with severe OSAS and reported EDS had the highest probability of requiring CPAP among individuals who underwent AT (50%) and children with severe OSAS without asthma or EDS had the lowest probability of requiring CPAP after AT (11%).

Lastly, we examined the effect of concomitant rhinitis in the link between asthma and need for CPAP therapy in children with severe OSAS after AT. Using a logistic regression model we found that the association between asthma and need of CPAP in children with prior AT due to severe OSAS was independent of rhinitis (adjusted OR = 3.16; 95% CI 1.63 to 6.15; $P = 0.001$). However, children with severe OSAS and both, asthma and rhinitis, had the highest probability of requiring CPAP among individuals who underwent AT (47%; Figure 4B).

4 | DISCUSSION

Pediatric OSAS is being recognized as an important public health problem,²⁴ which requires early diagnosis and treatment to prevent

adverse outcomes. Most common initial method of treatment is AT, but some children may require CPAP. Initiation of CPAP in children is challenging and the distinct features of the subset of children with severe obstructive sleep apnea syndrome (OSAS) that will require CPAP are still poorly defined. Asthma often coexists with OSAS in children²⁵ adding to overall morbidity. Previous researchers reported the impact of AT in children with OSAS and asthma.^{26,27} To date, there is lack of enough evidence about the influence of asthma on the need for CPAP in children with severe OSAS. In this study, we aimed to test the hypothesis that asthmatic children with severe OSAS have a higher probability of needing CPAP than children with severe OSAS without asthma.

In agreement with prior authors,²⁸ we found that asthma is very common in children with severe OSAS. Notably, in our current study we also observed that the requirement of CPAP was higher in children with severe OSAS and coexisting asthma. This association was significant even after adjusting for demographic factors, obesity and OSAS severity. In addition, asthma was also significantly associated with CPAP initiation in the subset of children who underwent AT. Together, these findings indicate the significance of identifying asthma as an important co-morbidity in pediatric OSAS that may increase the individual probability of needing CPAP therapy. While asthma is a respiratory condition associated with lower airway inflammation, there is growing evidence pointing to upper airway inflammation in OSA.²⁹ Indeed, we have reported that upper airway inflammation (rhinitis) influences the nocturnal OSA phenotype in children leading to more REM-related OSA.³⁰ In the present study, we also found that coexisting rhinitis and asthma required increased use of CPAP in children with severe OSAS. This upper/lower airway inflammatory synergism may potentially explain the increased morbidity and potential need for additional modes of treatment in children with OSAS and coexistent asthma.

Symptoms of OSAS including snoring, gasping arousal, observed apnea, and hyperactivity were comparable in children with and without asthma in our study. This is in contrast to prior studies showing the presence of asthma can worsen OSA symptoms.^{27,31} Interestingly, we found that the presence of asthma is associated with excessive daytime sleepiness (EDS) in children with severe OSAS. This is in agreement with previous studies that have identified a strong

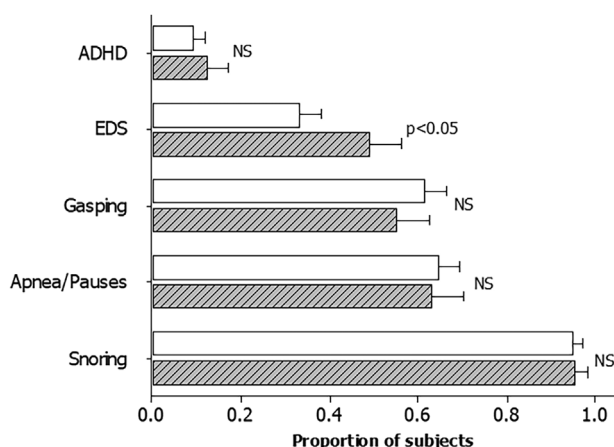


FIGURE 3 Comparison of the clinical presentation of all study subjects with severe OSAS ($n = 400$) including non-asthmatics (white bars) and asthmatics (gray bars). ADHD, attention deficit hyperactivity disorder; EDS, excessive daytime sleepiness

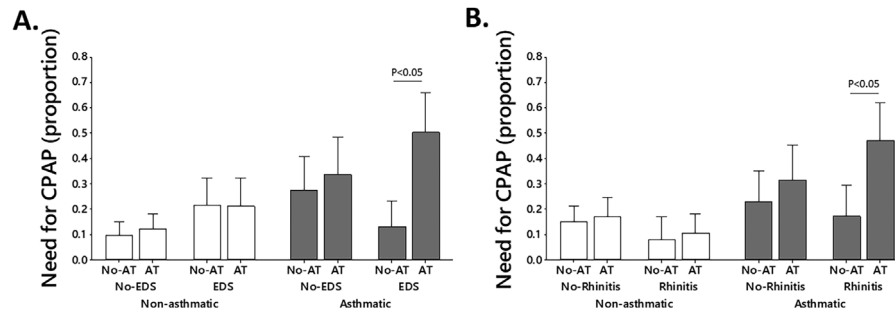


FIGURE 4 Comparison of the need for CPAP in non-asthmatics (white bars) and asthmatics (gray bars) according to adenotonsillectomy (AT) and: (A) the presence or absence of excessive daytime sleepiness (EDS); or (B) rhinitis. Data presented as 95% confidence intervals of the proportion of subjects

association between EDS and asthma.^{32,33} It has also been shown that both OSA and asthma can cause fragmented sleep in children.³² EDS in asthmatic patients can be potentially explained by an additive effect of nocturnal cough along with airway obstruction in OSA.³⁴ Further on, in our study, the presence of both asthma and EDS were significantly associated with the need for CPAP after AT compared to subjects without both conditions in pediatric severe OSAS. Collectively, these data suggest that better asthma control in these children may improve sleep quality, enhance day time functioning, and reduce the need for CPAP.

The strengths of this study included relatively large sample size and the use of objective data (PSG variables). In terms of limitations, the cross-sectional design prevented a definitive conclusion on the causative relationship between asthma and CPAP initiation in children with severe OSAS. The retrospective method of data gathering is subjected to selection and information bias resulting from inaccurate documentation in medical records. The latter limitation may be particularly relevant for children in the cohort who may have been seen outside the hospital for asthma related symptoms. Nonetheless, all patients included in the study had documentation of asthma status in the referral sleep study form. We included young children who have already been diagnosed to have asthma by a physician (we used the same criteria for all ages including the use of asthma therapy and/or presence of asthma symptoms in the past 12 months). We recognize that some of these children could in fact be transient wheezers who may not develop asthma symptoms later in life, however, given the lack of longitudinal data we decided not to exclude them from the study. The medical record data available did not allow us to obtain enough detail to accurately define asthma control or severity. This is an important limitation given that these parameters may be relevant variables to consider in asthmatic children with severe OSAS requiring CPAP therapy. Lastly, due to collinearity, oxygen saturation nadir and OAHl could not be simultaneously assessed in a multivariate model. Nevertheless, oxygen saturation nadir may be an important factor, in addition to the OAHl, in deciding which patients initiate CPAP therapy.

In summary, the presence of asthma was significantly associated with need for CPAP in children with OSAS. This association was stronger in the presence of daytime sleepiness or rhinitis. However, it is not clear if OSAS influences asthma control and the risk of asthma

exacerbation, or if controlling asthma decreases the risk for CPAP in pediatric OSAS. Thus prospective longitudinal studies are still required to further investigate the association between asthma diagnosis and the need of CPAP in children with OSAS.

CONFLICT OF INTEREST

None.

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